Evidence-based Antimicrobial stewardship , quo vadis?

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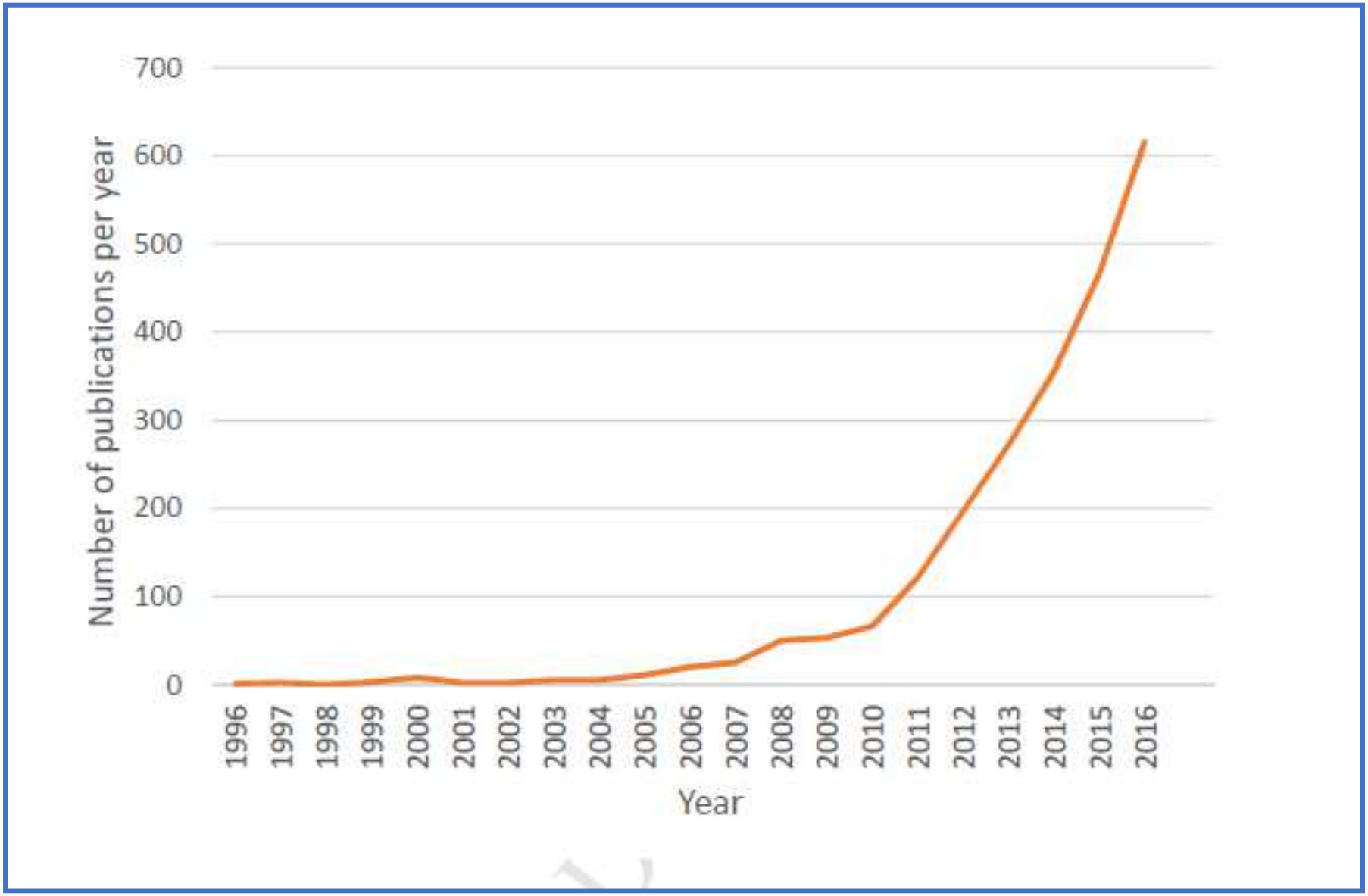


Dyar OJ, Huttner B, Schouten J, Pulcini C, on behalf of ESGAP (ESCMID Study Group for Antimicrobial stewardshiP), What is antimicrobial stewardship?, *Clinical Microbiology and Infection* (2017), doi: 10.1016/j.cmi.2017.08.026

What is an Antimicrobial Stewardship?

Refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

1. Minimize toxicity and other adverse events
2. Reduce the costs of health care
3. Limit the selection for antimicrobial resistant strains

IDSA, SHEA, PIDS; Infect Control Hosp Epidemiol 2012

Clinical Infectious Diseases

IDSA GUIDELINE

Strategies and challenges of antimicrobial stewardship in long-term care facilities

O. J. Dyar[1], L. Pagani[2] and C. Pulcini[3,4]

1) North Devon District Hospital, Barnstaple, UK, 2) Bolzano Central Hospital, Infectious Diseases Unit, Bolzano, Italy, 3) CHU de Nancy, Service de Maladies Infectieuses, and 4) Université de Lorraine, Université Paris Descartes, EA 4360 Apemac, Nancy, France

Implementing an Antibiotic Stewardship Program: Guidelin... and the ...

Antibiotic resistance

Review

1.7.2017 EN Official Journal of the European Union

Review

How can we improve antibiotic prescribing in primary care?

Oliver J. Dyar, Bojana Beović, Vera Vlahović-Palčevski, Theo Verheij & Céline Pulcini

Pages 403-413 | Received 23 Dec 2015, Accepted 03 Feb 2016, Accepted author version posted online: 06 Feb 2016, Published online: 24 Feb 2016

...als in human health

Chemotherapy

ELSEVIER

Veterinary Clinics of North America: Small Animal Practice

Volume 45, Issue 2, March 2015, Pages 361-376

Antimicrobial Stewardship in Small Animal Veterinary Practice: From Theory to Practice

Luca Guardabassi DVM, PhD [a], John F. Prescott VetMB, DVM, PhD [b]

...rdship programmes—what's missing?

...rani[1]*, Jonathan Cooke[2] and Alison Holmes[1]

...ent, Imperial College, London W12 OHS, UK; [2]University Hospital of South Manchester ...pital and Manchester Academic Health Science Centre, Manchester M23 9LT, UK

...wardship interventions

...bbas [1], B. Huttner [1, 2], S. Harbarth [1, 2]

Types of description of AMS	Examples from the literature
Descriptions of activities	Antimicrobial stewardship includes optimal selection, dose and duration of treatment, as well as control of antibiotic use [9] Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare professionals, and more specifically, to selection of the most appropriate antibiotic, duration, dose, and route of administration for a given patient[illegible]monstrated or suspected infection [36]
Descriptions of goals	The primary goal of antimicrobial stewardship is to optimize clinical outc[illegible]nces of antimicrobial use, including toxicity, the selection of pathog[illegible]
As a program or set of interventions	AMS refers to coordinated interventions [illegible]y promoting the selection of t[illegible] administration [1[illegible] An[illegible]through promotion of [illegible]nitor and direct antimicrobial use at a healthcare to judicious antimicrobial use [1] [illegible]administration and duration of antimicrobial therapy [39]
As an ap[illegible]	[illegible]to the multifaceted approach (including or method policies, guidelines, surveillance, prevalence [illegible]and audit of practice) that healthcare organizations have adopted to optimize prescribing [40] [illegible]crobial stewardship is a method of overseeing antimicrobial use in healthcare facilities to ensure that every patient requiring antimicrobial therapy receives optimal therapy [22]
As a means to tackle resistance	Antimicrobial stewardship is a key component of a multifaceted approach to preventing emergence of antimicrobial resistance [41] A proposed solution to the combined problems of increasing antibiotic resistance, the dwindling number of antimicrobial agents, and the suboptimal use of antibiotics in clinical practice is the strategy of antimicrobial stewardship [38] A critical mission of preservation of antimicrobial utility [39]
As responsible use	Antimicrobial stewardship programs are a set of interventions that aim to ensure the judicious use of antimicrobials by preventing their unnecessary use, and by providing targeted and limited therapy in situations where they are wanted [42] [Stewardship] refers to how the judicious use of antibiotics can maximize both their current effects and the chances of their being available for future generations [18]
Descriptions of good stewardship	Good antimicrobial stewardship is the optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance. Good antimicrobial stewardship is akin to motherhood and apple pie [24] Good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while minimizing toxicity and conditions for selection of resistant bacterial strains [41]

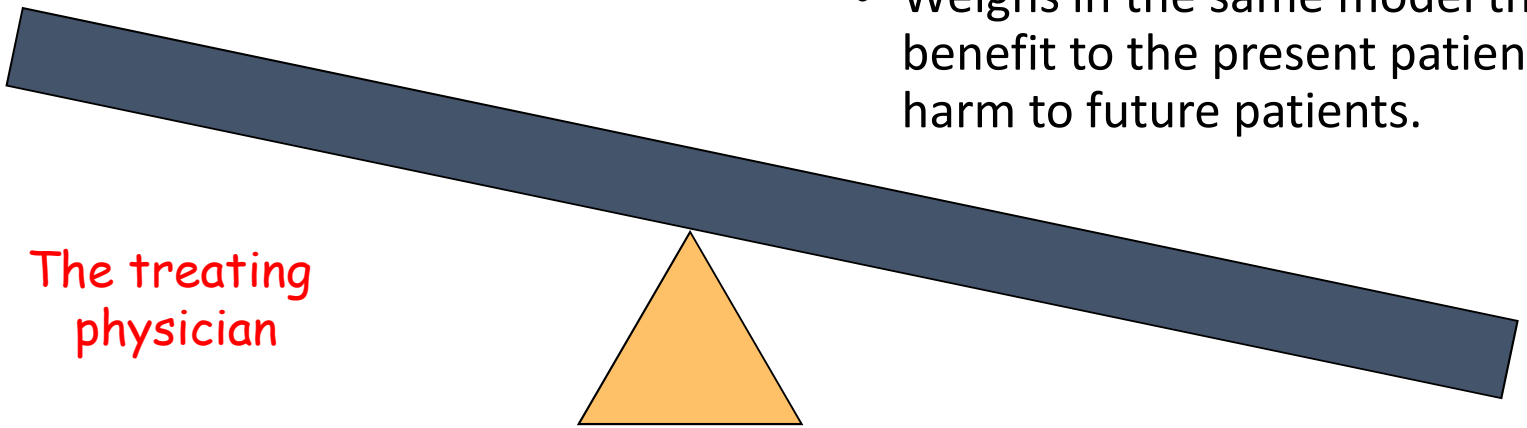
Which is the difference with being a reliable ID / CM?

Dyar OJ, Huttner B, Schouten J, Pulcini C, on behalf of ESGAP (ESCMID Study Group for Antimicrobial stewardshiP), What is antimicrobial stewardship?, *Clinical Microbiology and Infection* (2017), doi: 10.1016/j.cmi.2017.08.026

Tension between the present patient and future patients

- Prescribes antibiotics for the present patient

- Takes responsibility for all (present and future) patients
- Weighs in the same model the benefit to the present patient vs harm to future patients.



courtesy of Prof. M. Paul

Tragedy of the Commons

William Forster Lloyd (1833), Garrett Hardin (1968)

The pursuit of individual gain leads to abrogation of the common good.

Lloyd was familiar with herdsmen who all grazed their cattle on a **commons**. Each individual gained by adding more cows to his own herd. As each pursued his individual gain, the commons became overgrazed, resulting in the tragedy malnourished cows.

- Each person acts in his self interest, overlooking the fact that overuse of a resource may in the end destroy it
- Depletion of resources owned collectively

Science 1968, courtesy of Prof. M. Paul

Determinants of antibiotic prescribing in hospitals

Journal of Antimicrobial Chemotherapy

Theme	Comment
1. Decision-making autonomy	*'Sometimes during a procedure, if the surgeon feels there's a need to introduce antibiotics, they say so and I have never challenged that, no one has ever challenged that.'* Nurse, Orthopaedics (12 years)
2. Limitations of local evidence-based policies	*'Sometimes it is difficult to…use the policy because the policy will be your average sort of thing, it's not looking at someone at the top or at the bottom.'* Pharmacist, General Medicine (2 years)
3. Culture of hierarchy	*'The junior doctors tend to change it and the junior doctors won't change it if their senior doctors, if the consultant or registrar's specifically asked them to prescribe something else.'* Pharmacist, ICU (7 years)
4. Etiquette	*'I think doctor to doctor, it's very difficult for clinician to clinician, especially different specialties to go and criticize one another. I think that's not collegial practice, so people don't want to do that.'* Nurse, Outpatient Parenteral Antimicrobial Therapy Services (14 years)

Modified from data in Charani et al., JAC 2015

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Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S

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INTERVENTIONS INCLUDED

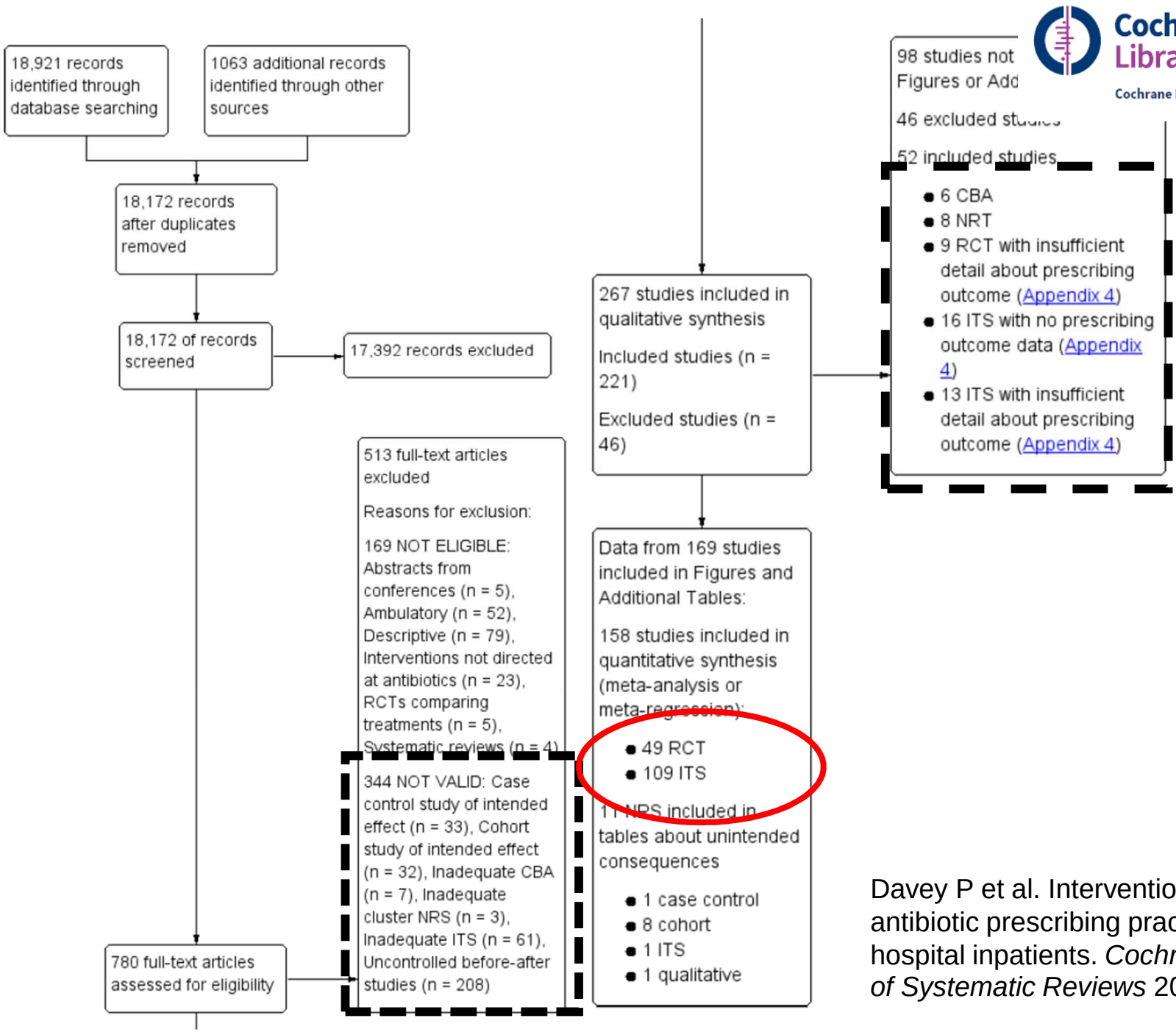
- **Audit and feedback**
- **Educational** intervention (meetings, academica **ENABLING INTERVENTION** f single patien
- **Reminders** (verbals, printed)
- Structural (switch to computerized records, new diagnostic technologies)
- **Restriction** (selective lab reporting, form oval, **RESTRICTIVE INTERVENTION** automatic stop, theraputic substitution)

OUTCOMES EVALUATED

1) Compliance with guidelines or policies, duration of treatment, decision to treat

2) Mortality, lenght of stay, microbial outcomes
Unintended-consequences (delay in start of treatment…)

Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews* 2017



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SUMMARY OF FINDINGS (only RCTs):

Effectiveness: prescribing outcomes from RCTs

Outcomes	Absolute effect*		No of participants (No of studies)	Certainty of the evidence (GRADE)	Comments
	Without intervention	With intervention			
Proportion of participants who were treated according to antibiotic prescribing guidelines Follow-up to end of study	43 per 100	58 per 100	23,394 participants (29 RCTs)	⊕⊕⊕⊕ High	We have graded the certainty of evidence as high because het-
	Difference: 15 more participants per 100 (95% CI 15 to 23) received appropriate treatment following intervention				a similar result (RD 11%, 95% CI 10% to 12%)
Duration of all antibiotic treatment	11.0 days	9.1 days	3318 participants (14 RCTs)	⊕⊕⊕⊕ High	
	Difference: 1.95 fewer days per participant (95% CI 2.22 to 1.67)				
Mortality Follow-up to end of study	11 per 100	11 per 100	15,827 participants 28 (RCTs)	⊕⊕⊕◯[1] Moderate	Mortality and length of stay were
					sure

+ 15% appropriately treated

- 2 days of ABT treatment

NO CHANGES IN MORTALITY

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SUMMARY OF FINDINGS (RCT/ITS)

Mean length of hospital stay per participant	12.9 days 11.8 days Difference: 1.1 fewer days per participant (95% CI 1.5 to 0.7 fewer)	3834 participants 15 (RCTs)	⊕⊕⊕◯[1] Moderate	interven- studies
Delay in treatment	Restrictive interventions increased the risk of delay in all 3 studies. The risk to patients resulted in termination of the RCT by the Trial Monitoring Committee	1 RCT, 2 cohort	⊕⊕◯◯[2] Low	The evidence from these 7 studies of unintended consequences raises concerns about the directness of the evidence of safety from the 29 RCTs in the previous section of the table (see above)
Negative professional culture	Loss of trust in infection specialists because of failure to record approvals for restricted drugs or provide warning about stopping treatment Misleading or inaccurate information from prescribers in order to meet criteria for restricted drugs. In 1 hospital, misdiagnosis of hospital-acquired infection was large enough to trigger an outbreak investigation	1 case control, 2 cohort, 1 qualitative	⊕⊕◯◯[3] Low	
Effect modifiers (heterogeneity) for immediate effect of intervention on prescribing outcomes: impact of behaviour change functions (enablementor restriction) and additional impact of feedback, RCTs and ITS studies. A positive value for Beta means the modifier is associated with increased effect				

- 1 day in hospital

Can have some uninteded consequences

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Both enabling and restriction work…..

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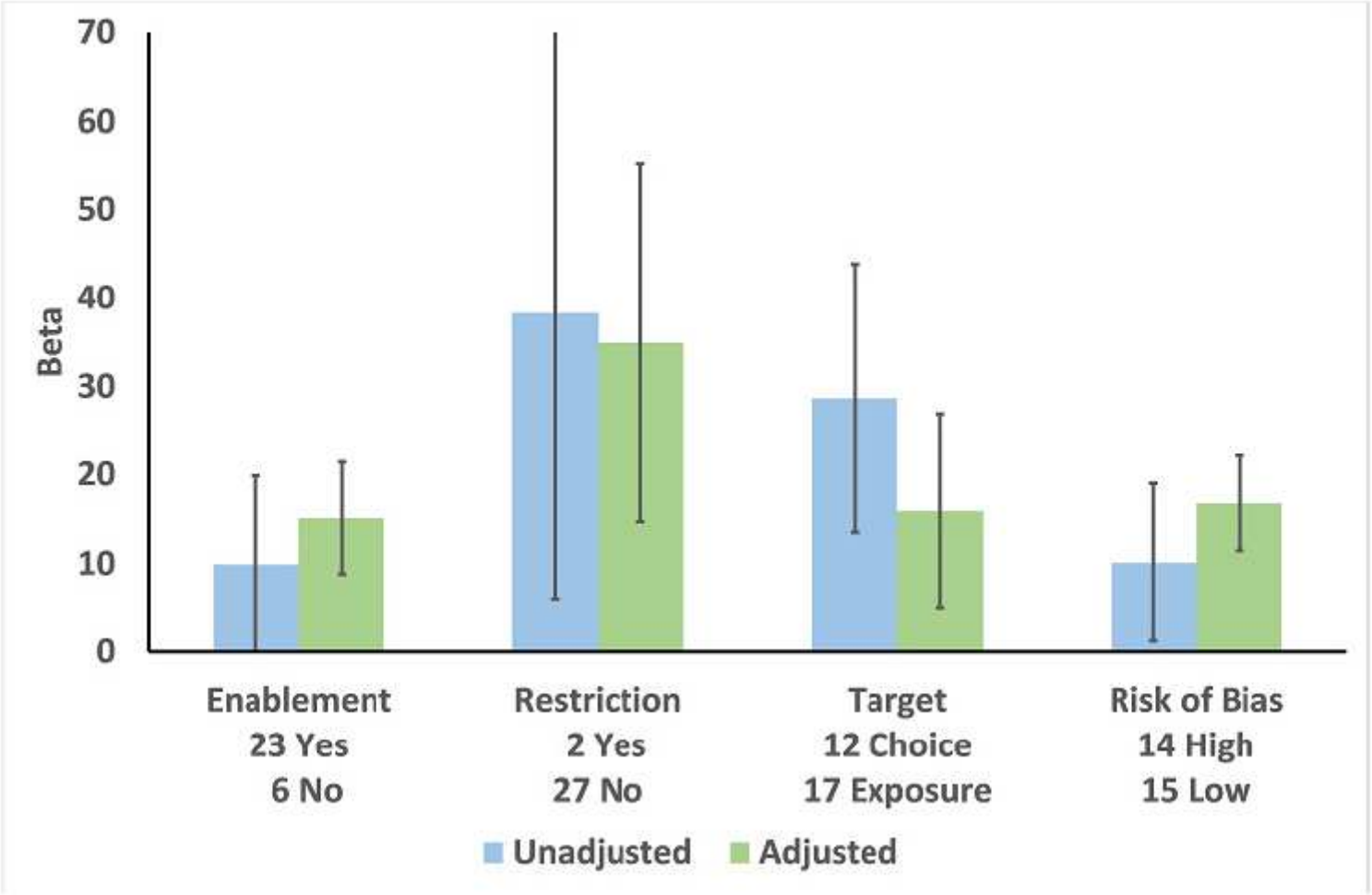
Figure 7. Meta-regression by effect modifier for 29 RCTs. A positive value for Beta indicates enhanced intervention effect. One RCT had both enabling and restrictive components in the intervention (Strom 2010).



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Feedback adds something…

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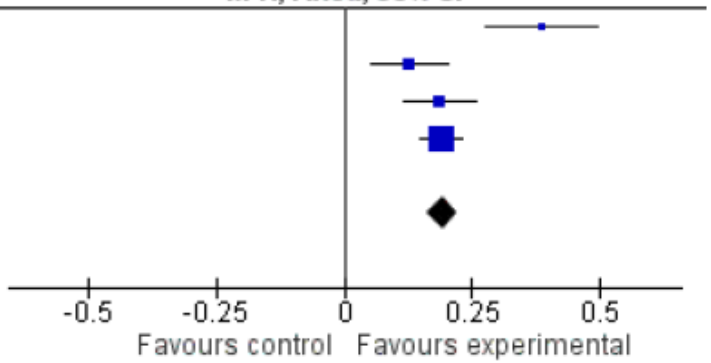
Figure 8. Forest plot of comparison 5: RCTs of enablement with and without feedback, outcome: 5.1 Enablement plus feedback.

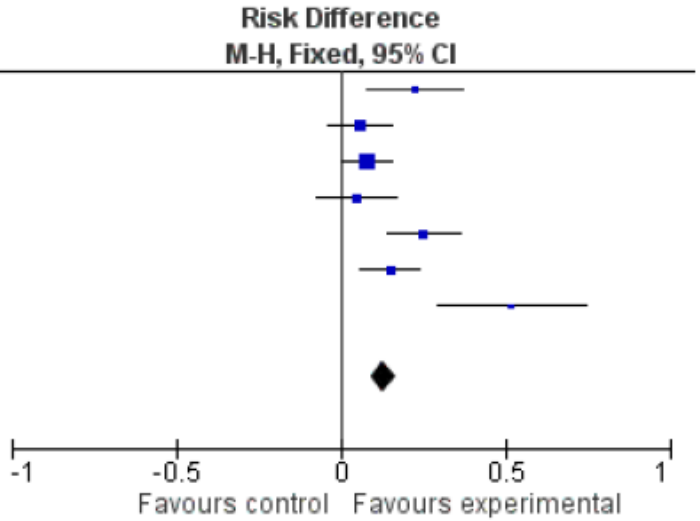
Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Camins 2009	92	112	60	138	6.8%	0.39 [0.28, 0.50]
Schnoor 2010	182	275	186	348	16.8%	0.13 [0.05, 0.20]
Schouten 2007	296	460	154	338	21.4%	0.19 [0.12, 0.26]
Yealy 2005	631	849	677	1227	55.0%	0.19 [0.15, 0.23]
Total (95% CI)		**1696**		**2051**	**100.0%**	**0.19 [0.16, 0.22]**
Total events	1201		1077			

Heterogeneity: Chi² = 14.98, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 12.39 (P < 0.00001)



Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Burton 1991	58	70	44	73	7.8%	0.23 [0.08, 0.37]
Dranitsaris 2001	122	162	102	147	16.9%	0.06 [-0.04, 0.16]
Paul 2006	216	297	176	273	31.2%	0.08 [0.01, 0.16]
Senn 2004	80	126	73	125	13.8%	0.05 [-0.07, 0.17]
Solomon 2001	88	125	69	153	15.1%	0.25 [0.14, 0.37]
Trenholme 1989	102	110	90	116	12.4%	0.15 [0.06, 0.24]
Walker 1998	22	25	9	25	2.7%	0.52 [0.29, 0.75]
Total (95% CI)		**915**		**912**	**100.0%**	**0.13 [0.09, 0.17]**
Total events	688		563			

Heterogeneity: Chi² = 22.90, df = 6 (P = 0.0008); I² = 74%
Test for overall effect: Z = 6.26 (P < 0.00001)



Study conclusions, further research

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- NOT focus on improvement of prescripition policy (unlikely to change this results)

- Better focus on intervention types reflecting Behavioural Changing Techniques (EPOC)

- Better focus on other outcomes (CLINICAL AND MICROBIOLOGICAL)

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Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

David Baur, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli*

Patient

Hospitalized adult patients

Intervention

Implementation of any ASP

Comparison

no intervention

Outcome

Reduction in

- **Incidence of AMR (infection/colonization)**
- ***C. difficile* infections**

Tacconelli et al, Lancet Infect Dis 12 June 2017

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Effect size calculation:
Incidence Rate Ratio of antimicrobial resistance

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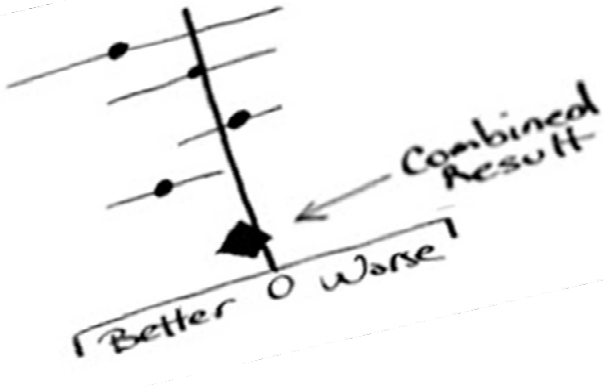
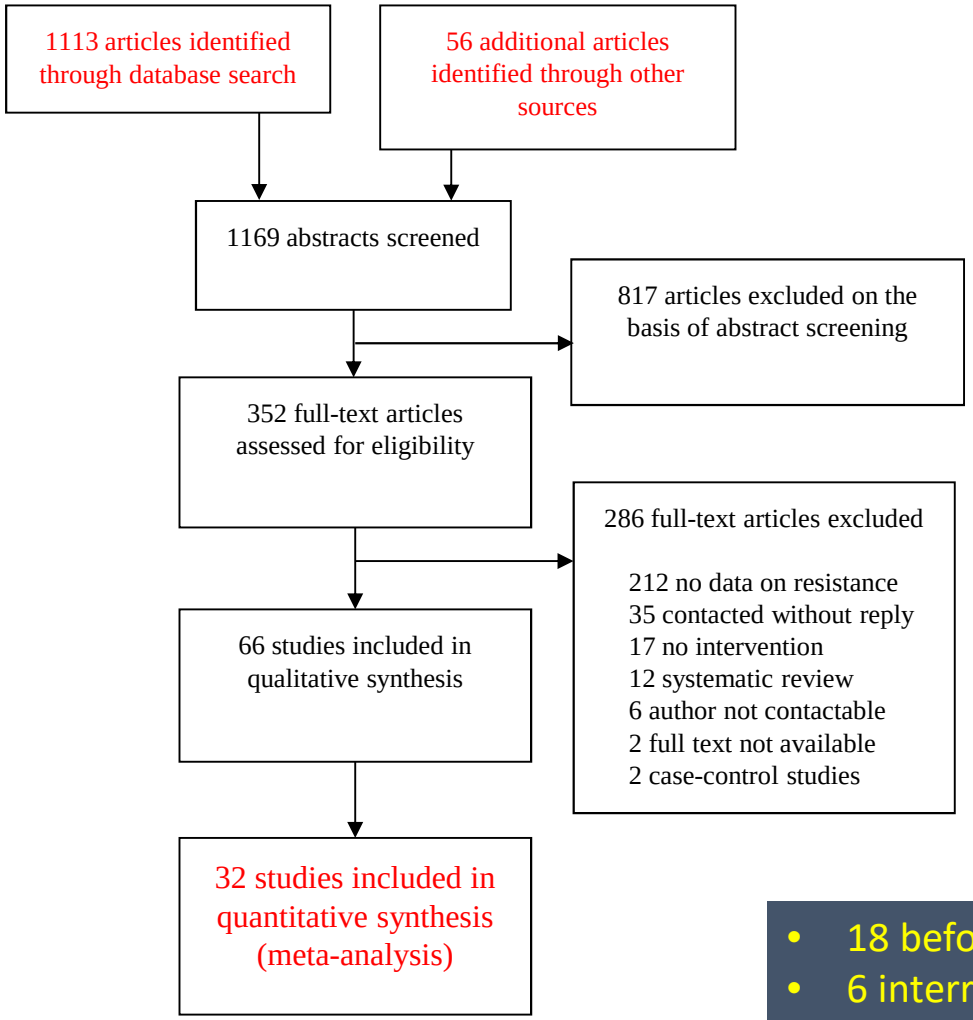
$$\frac{\text{AMR infections-colonization and } \textit{C.difficile} \text{ infection } \textbf{per PDs with ASPs}}{\text{AMR infections-colonization and } \textit{C.difficile} \text{ infection } \textbf{per PDs without ASPs}}$$

<1 favors the intervention



Tacconelli et al, Lancet Infect Dis 12 June 2017

Flow chart of the systematic review

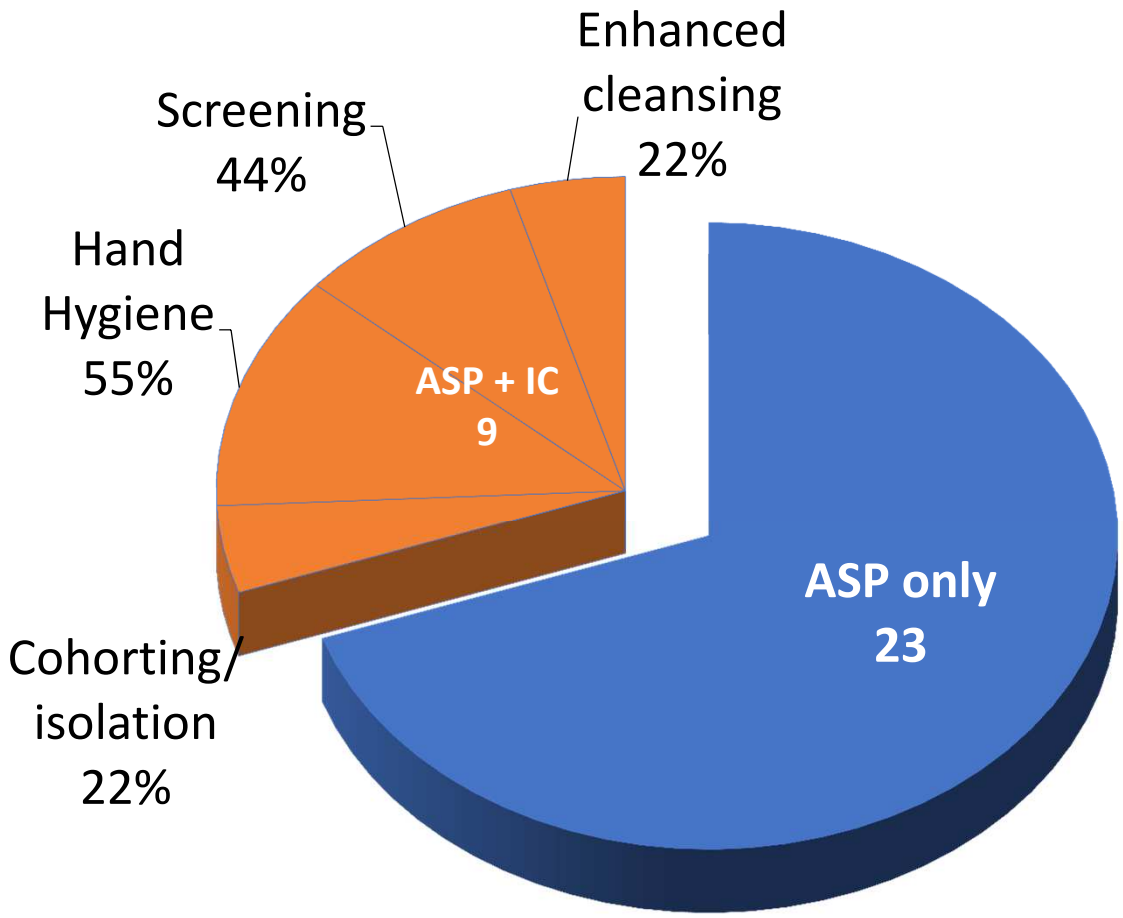


- 18 before-after studies
- 6 interrupted time series studies
- 7 cohort studies
- 1 nested case-control study

Tacconelli et al, Lancet Infect Dis 12 June 2017

Type of interventions

15	Restrictive use
19	Audit and feedback
5	Guidelines
3	Antibiotics cycling



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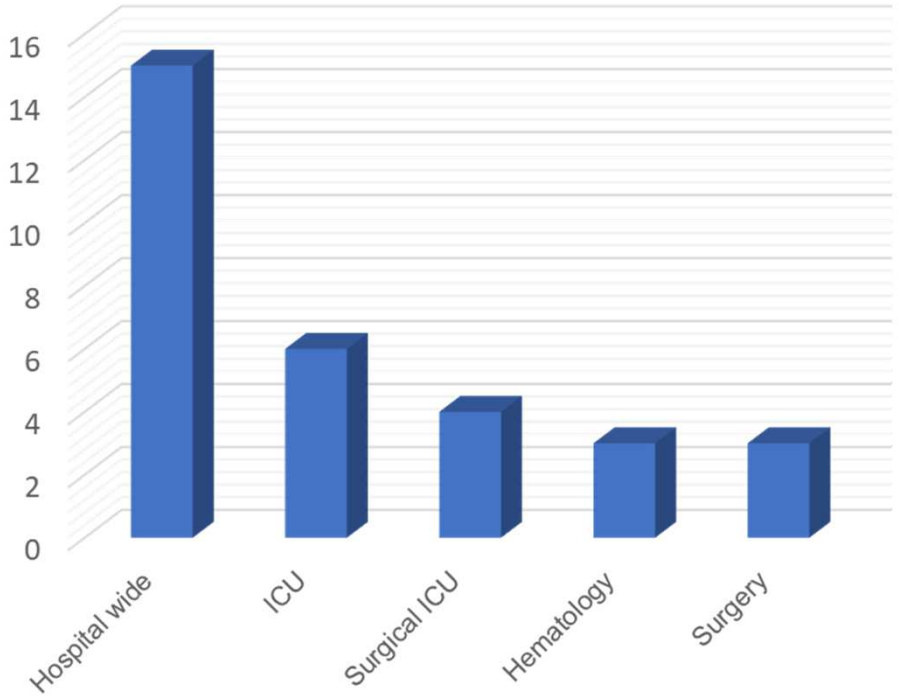
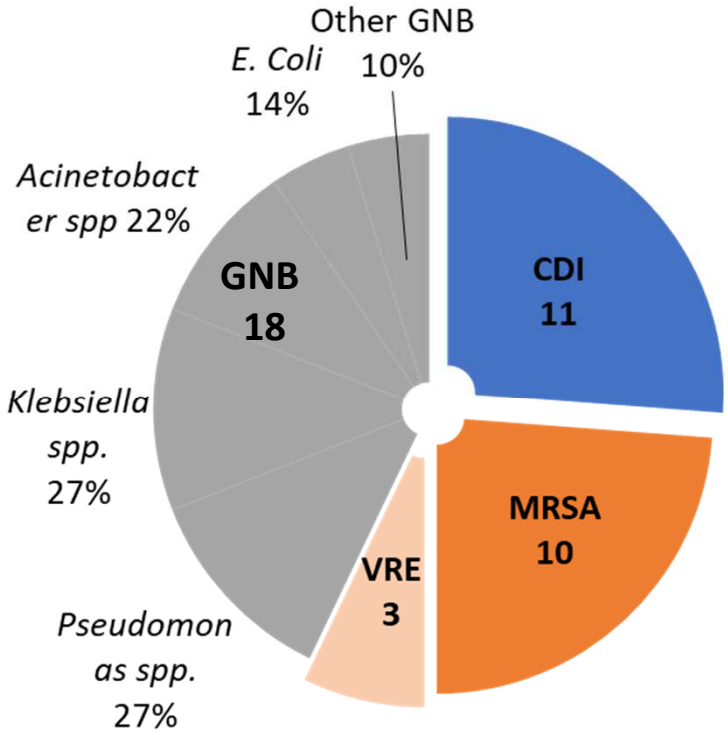
Study characteristics

- **Time period: 1997- 2014**
- **20 countries**
- **9 056 241 patient-days and 159 IRR estimates**





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Study results – overall analysis

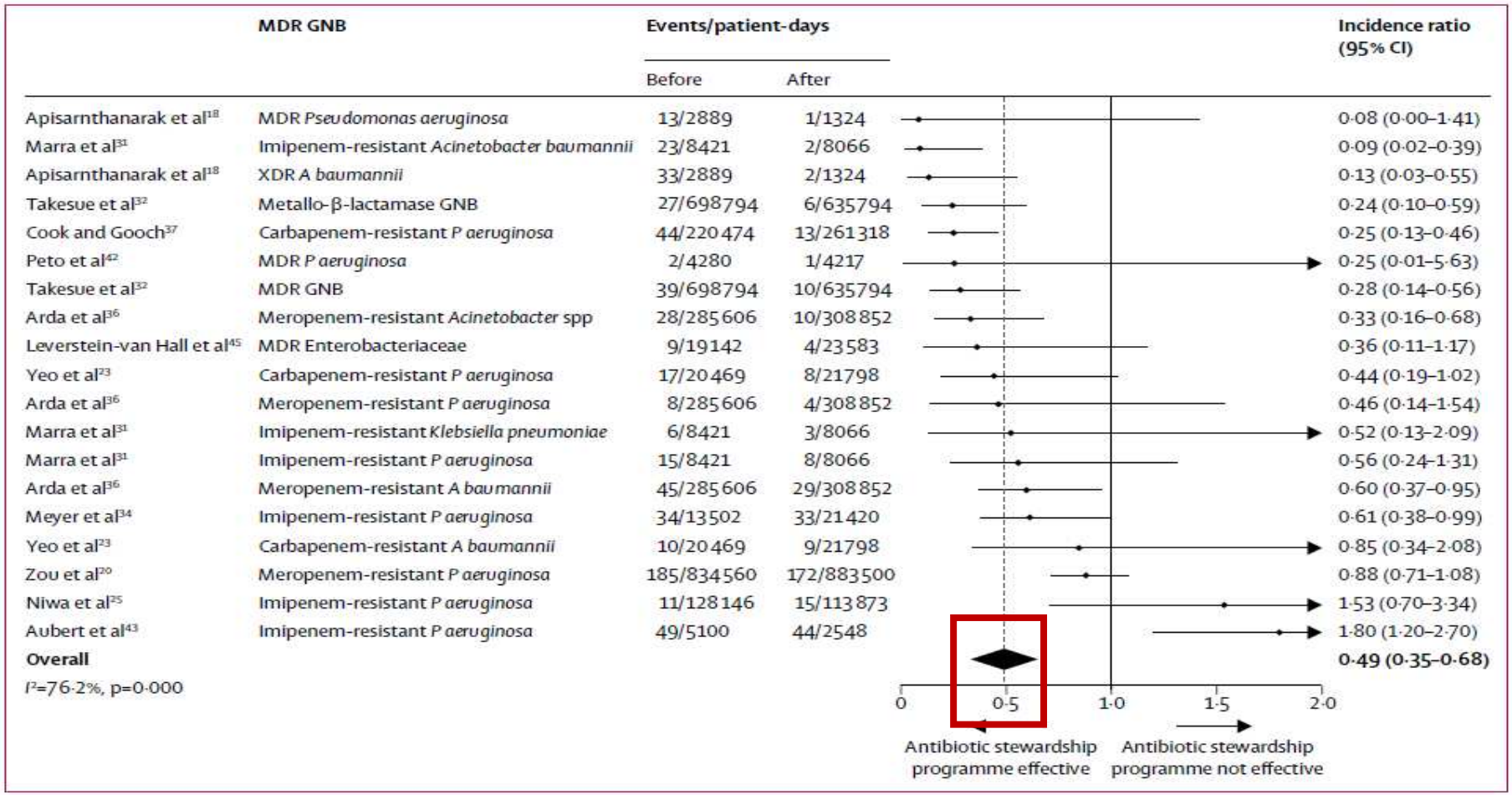
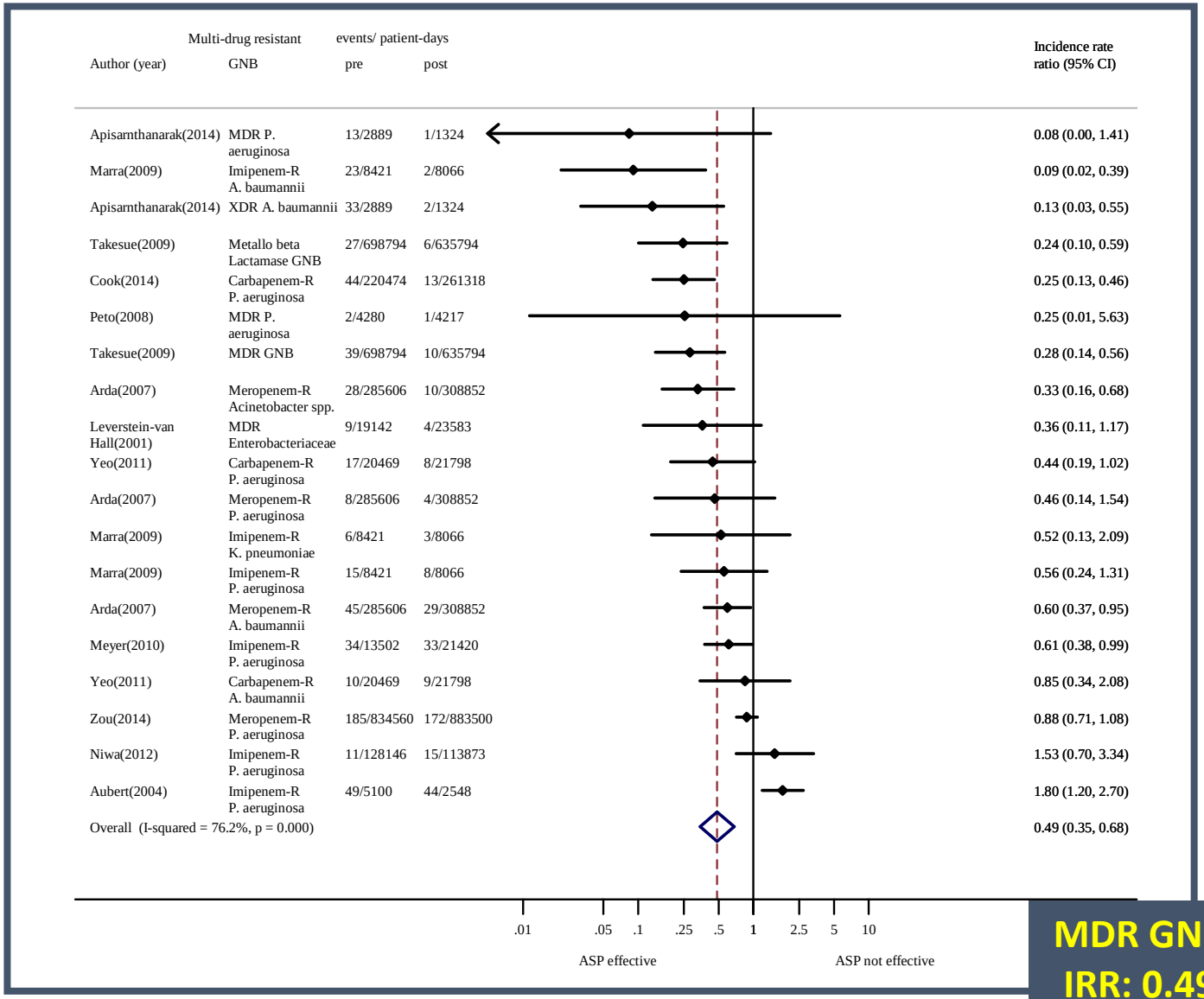


***Figure 2*: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB**
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

Tacconelli et al, Lancet Infect Dis 12 June 2017

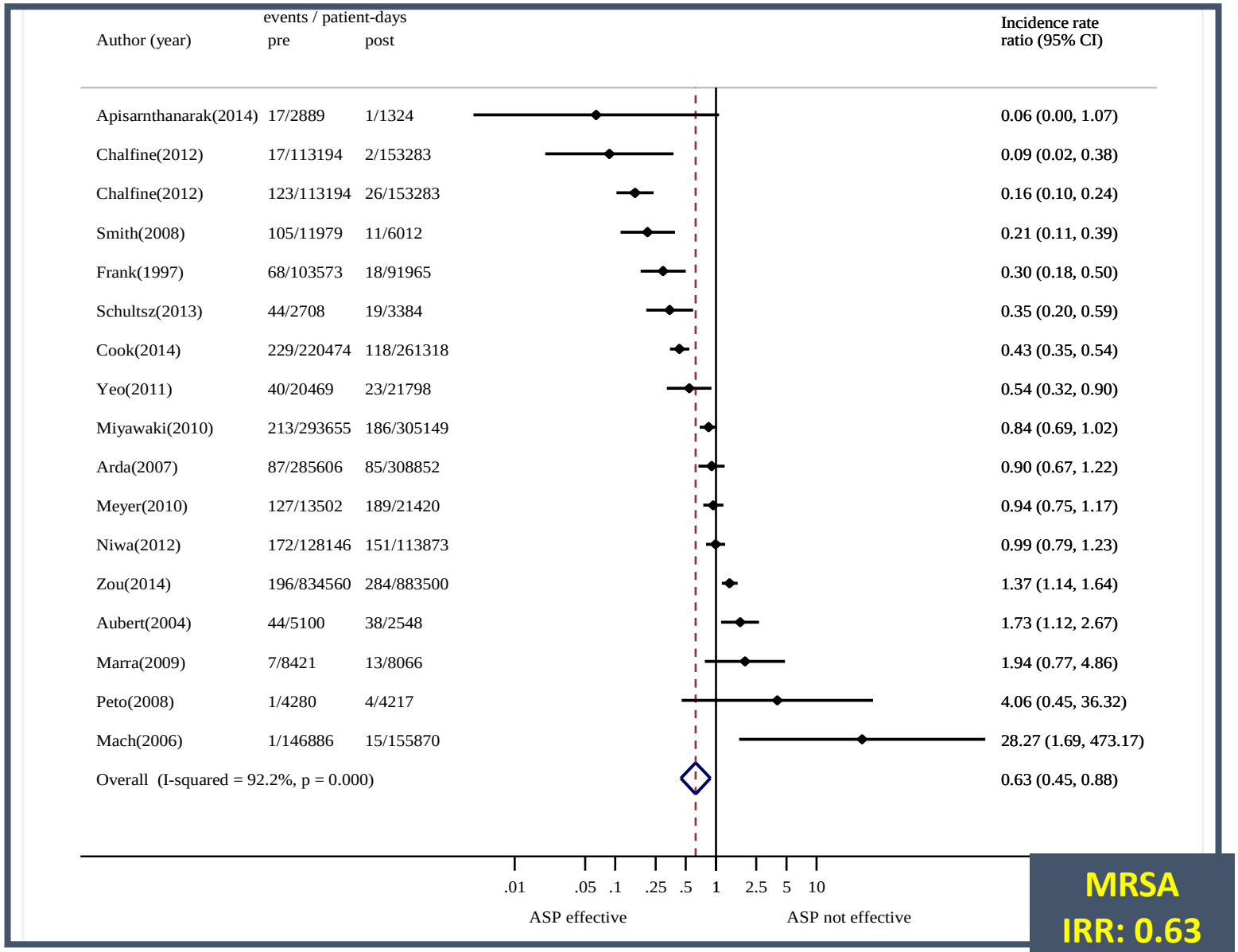
Results: incidence of multidrug-resistant gram-negative bacteria



MDR GNB
IRR: 0.49
(0.35-0.68)

Tacconelli et al, Lancet Infect Dis 12 June 2017

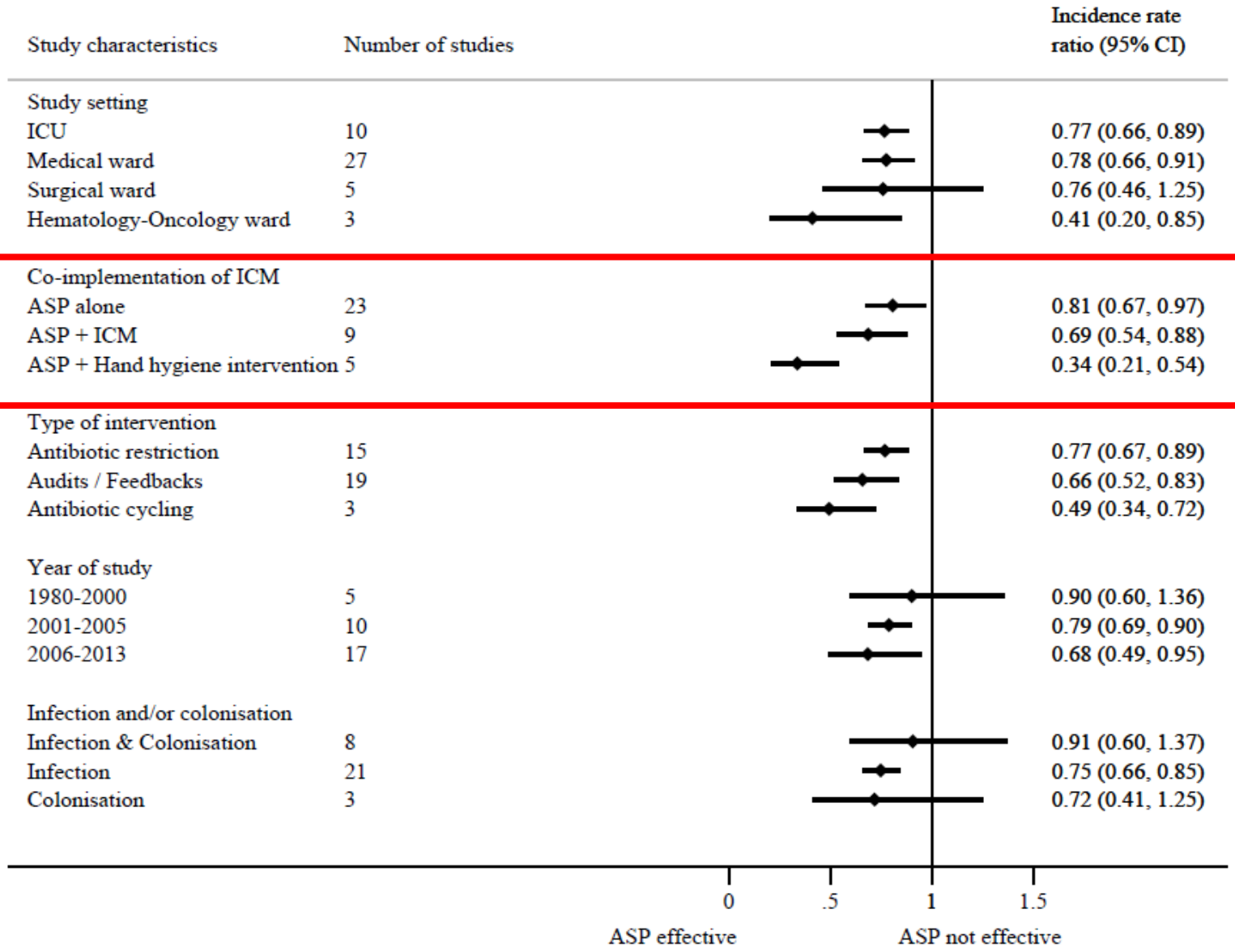
Results: incidence of methicillin-resistant *Staphylococcus aureus*



MRSA
IRR: 0.63
(0.45-0.88)

Tacconelli et al, Lancet Infect Dis 12 June 2017

Results: subgroup analysis



Evidence-based Antimicrobial stewardship , quo vadis?

Clinica

L'antimicrobial stewardship è efficace nel migliorare l'appropriatezza prescrittiva e deve essere implementata su multipli livelli (comunità. Ospedale, LTCF, veterinaria…);

ASP ed IC si potenziano a vicenda e sono entrambi colonne portanti della lotta contro le infezioni da AMR.

Ricerca

Studi futuri devono chiarire meglio quali tecniche sono più efficaci nel migliorare l'appropriatezza prescrittiva;

Studi futuri devono avere *design* rigorosi (RCT, ITS controllati) per cercare di limitare al massimo il rischio di bias in interventi complessi;

Per misurare l'efficacia dell'ASP servono outcome migliori ed innovativi che comprendano il rischio/beneficio del singolo paziente e della comunità

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- **Head Investigator:** Prof Evelina Tacconelli
- **Physicians:** Stefanie Döbele, Federico Foschi, Elena Carrara, David Baur, Francesco Burkert
- **Scientist:** Primrose Beryl







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